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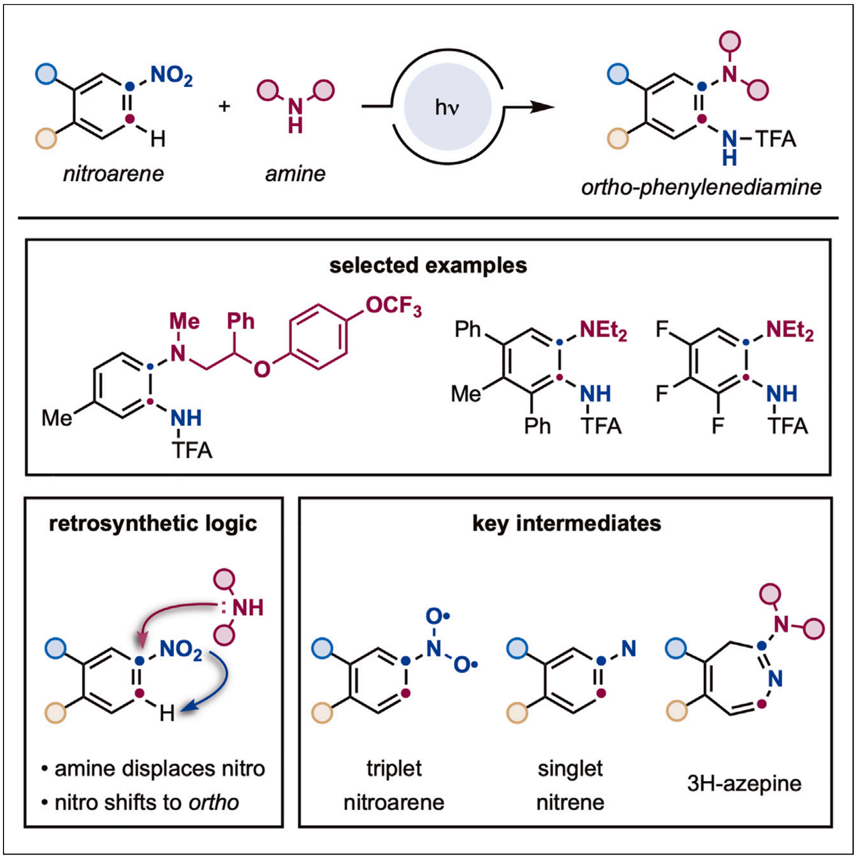
alessandro.ruffoni@rwth-aachen.de (A.R.)
daniele.leonori@rwth-aachen.de (D.L.)



Ortho-phenylenediamines are high-value molecules generally prepared using multistep synthetic sequences. Here, we demonstrate that they can be assembled in one chemical step from nitroarenes upon visible-light irradiation. This strategy simplifies the preparation of complex materials and features a temporary disruption of the nitroarene aromaticity, followed by amination and reconstruction of the aromatic framework.

Highlights

Photochemical synthesis of *ortho*-phenylenediamines from nitroarenes

Triplet nitroarenes are converted into singlet nitrenes upon irradiation

Singlet nitrenes enable direct amination of nitroarenes via de-aromatization

Sánchez-Bento et al., Chem 9, 3685–3695
December 14, 2023
https://doi.org/10.1016/j.chempr.2023.10.008

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A strategy for *ortho*-phenylenediamine synthesis via dearomative-rearomative coupling of nitrobenzenes and amines

Raquel Sánchez-Bento,[1,4] Baptiste Roure,[1,4] Josep Llaveria,[2] Alessandro Ruffoni,[3,*] and Daniele Leonori[3,5,*]

SUMMARY

Ortho-phenylenediamines are aromatic molecules featuring two vicinal _N_-substituents with strong structural relevance to the development of bioactive materials. These derivatives are currently prepared from _ortho_-halogenated nitrobenzenes via multistep synthetic sequences. Here, we report a conceptually different approach where nitrobenzenes and amines can be directly converted into _ortho_-phenylenediamines without the need for _ortho_-halogenation and following stepwise synthetic manipulation. This strategy occurs under simple blue light irradiation and introduces an alternative retrosynthetic tactic whereby the amine coupling partner "seems" to displace the nitro group that shifts to its _ortho_ position while being reduced and amidated in a one-pot process. Mechanistically, this process capitalizes on the conversion of nitrobenzenes into the corresponding single nitrenes, which undergo a series of _N_-insertion, electrocyclic ring expansion, amine addition, and electrocyclic ring contraction en route to the _ortho_-phenylenediamines.

INTRODUCTION

The introduction of amine functionalities onto aromatic rings is one of the most frequent tasks in synthetic and medicinal chemistry. Because anilines are widespread in the core structure of bioactive materials, methods that streamline their preparation can positively impact our society. Among all types of nitrogenated aromatics, an important yet difficult-to-access class of derivatives is represented by the *ortho*-phenylenediamines (Scheme 1A). These compounds are found in many blockbuster drugs and feature two vicinal *N*-based functionalities, often at different oxidation states (e.g., amine and amide/carbamate).[1–4] Synthetic approaches toward these derivatives are generally based on the preparation of *ortho*-halo-nitrobenzenes **C** (X = F or Cl) by either halogenation[5] or nitration[6,7] of, respectively, benzene derivatives **A** and **B** (Scheme 1B). Ensuring *ortho*-selectivity in these processes can often be difficult, especially when the aromatic substitution pattern cannot be used to leverage electrophilic aromatic substitution chemistry (S_EAr).[8] Furthermore, once **C** is accessed, a multistep sequence involving (1) nucleophilic aromatic substitution (S_NAr)[9] with an amine followed by (2) nitro group reduction and (3) additional functionalization (e.g., amine construction or amide synthesis) is required to access **D**.[10,11] Overall, current approaches for the construction of *ortho*-phenylenediamines require solving the challenges of aromatic siteselectivity and follow synthetic sequences of a minimum of four steps.[12]

In addition to these synthetic challenges, it is interesting to note how the over-reliance on this single synthetic approach has biased the structural diversity of known

THE BIGGER PICTURE

Ortho-phenylenediamines are motifs often found in the structure of high-value materials, such as drugs. These molecules feature two nitrogen substituents connected to an aromatic ring in an *ortho* arrangement. Traditional manufacturing methods introduce the first nitrogen via nitration, which is followed by multistep syntheses, owing to the challenges associated with installing amines in place of aromatic C–H bonds. This article describes a different strategy that simplifies the preparation of these molecules directly using nitroarenes in one single chemical step. Mechanistically, this is achieved by converting the nitro group into a singlet nitrene by low-energy visible-light irradiation. This species starts a cascade process that temporarily disrupts the aromaticity so that an amine can be introduced and then re-aromatizes the substrate. The net result is that the amine has displaced the nitro group, which itself is shifted to its *ortho* position, reduced, and functionalized.

ortho-phenylenediamines. Indeed, substrates containing a complex amine substituent (labeled as N^1), usually feature it at the aromatic position activated for S_NAr reactivity (**D**, Scheme 1B). This is because a direct substitution reaction with an often-commercial amine is synthetically more convenient than embarking into a multistep synthetic endeavor across the nitro group. The retrosynthetic implication of this is that in order to access *ortho*-phenylenediamine isomer **F**, one must switch the substitution pattern of the initial *ortho*-halo-nitrobenzene (**E**, Scheme 1B), something often difficult to achieve.[13] Alternative approaches based on aromatic C–H activation/functionalization with metals or radical species, respectively, have been reported in recent years, partially mitigating some of these issues.[14–20] However, the installation and removal of directing groups on the free anilines, accessed by nitration and reduction, can limit the applicability of these methodologies, especially in terms of step count.

In this paper, we present a methodology that helps address many of the challenges mentioned above. The strategy reported here enables the direct coupling of nitrobenzenes (**A**) with complex primary and secondary amines to access *ortho*-phenylenediamines (**F**) without the need for aromatic pre-functionalization (**C**) and multistep nitro group manipulation (Scheme 1C). This is achieved by using a photochemical approach that bypasses the selectivity rules of aromatic substitution chemistry and "visually" introduces the amine substituent in place of the nitro group. Furthermore, the nitro group is seemingly undergoing a 1,2-positional switch across the aromatic core while being reduced and functionalized in one operation. Overall, this strategy provides a significantly shorter entry into *ortho*-phenylenediamines and, crucially, offers a convenient retrosynthetic disconnection to access difficult-to-make isoforms **F** under mild reaction conditions.

RESULTS AND DISCUSSION

Reaction design and development

In approaching the development of a different strategy for *ortho*-phenylenediamine synthesis, we were interested in harnessing the ability of aryl nitrenes to alter the structure of aromatic compounds, in concert with the power of 6π-electrocyclic reactions to ring-open and ring-close high-energy intermediates.[21,22] Specifically, we recognized the inherent advantages of converting a stable nitroarene (e.g., *para*-nitro-toluene, **1a**) into the corresponding and high-energy singlet nitrene **I** for a facile dearomative *N*-atom ring insertion process (Scheme 1D).[23] This reaction would provide, in the presence of an amine coupling partner (e.g., Et_2NH), a 3*H*-azepine intermediate **VI**. In a single pioneering example from 1973, Lambert demonstrated that such high-energy intermediates might undergo re-aromatization to *ortho*-phenylenediamine, upon treatment with benzyl chloride at high temperature.[24] Because this chemistry has not been explored any further, achieving our proposal required solving several challenges, starting with the key singlet nitrene generation. Indeed, aryl nitrenes have been classically generated by high-energy irradiation of aryl azides (often under cryogenic conditions, e.g., −78°C), something difficult to put forward considering the low commercial availability of these derivatives and their often-explosive profile.[25,26] Alternatively, Cadogan in the 1970s demonstrated that nitroaromatics can be sequentially deoxygenated to the corresponding nitrenes using phosphorous reagents, but under rather harsh and unpractical conditions (phosphite and amine as the solvent, T > 120°C).[27–29] It is important to note that, while we were finalizing our work, Radosevich disclosed an alternative take on Cadogan-Lambert reactivity using a catalytic P(V) reagent and a stoichiometric silane.[30]

[1] Department of Chemistry, University of Manchester, Manchester M13 9PL, UK

[2] Global Discovery Chemistry, Therapeutics Discovery, Janssen Research & Development, Janssen-Cilag S.A., Jarama 75A, 45007 Toledo, Spain

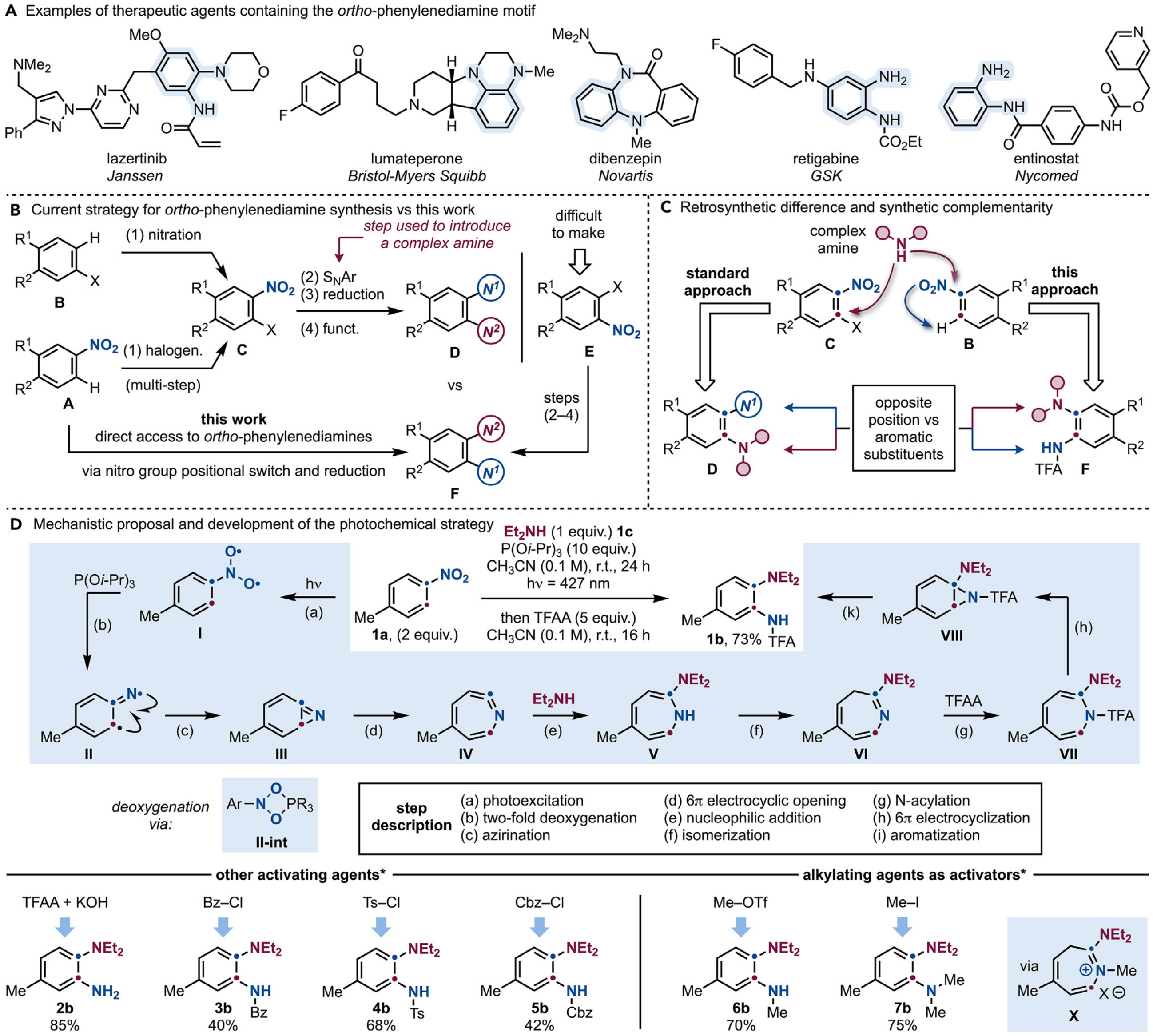
[3] Institute of Organic Chemistry, RWTH Aachen University, Aachen 52056, Germany

[4] These authors contributed equally

[5] Lead contact

*Correspondence:
alessandro.ruffoni@rwth-aachen.de (A.R.),
daniele.leonori@rwth-aachen.de (D.L.)

https://doi.org/10.1016/j.chempr.2023.10.008



Scheme 1. Relevance of *ortho*-phenylenediamines and their synthesis

(A) Examples of commercial medicines featuring the *ortho*-phenylenediamine motif.

(B) Current strategies for *ortho*-phenylenediamine synthesis rely on S_EAr chemistry to assemble *ortho*-halogenated nitrobenzenes and then require additional multistep sequences centered on S_NAr amination. This work provides streamlined access to *ortho*-phenylenediamine without nitrobenzene halogenation and multistep elaboration. X, halogen.

(C) This strategy provides a different tactic for *ortho*-phenylenediamine synthesis as the amine nucleophile "appears" to substitute the nitro group.

(D) Proposed mechanistic pathway for the conversion of nitrobenzene **1a** and amine **1c** into *ortho*-phenylenediamine **1b** and additional scope for N-functionalization in the products. *, reactions performed on isolated **VII**.

Our blueprint for aryl nitrene generation from nitroaromatics was instead based on the use of low-energy visible-light-mediated photoexcitation. Because the absorption profile of nitroarenes tails off in visible region, we postulated that simple irradiation with blue light would populate (after intersystem crossing) their corresponding triplet excited state (I).[31] Triplet nitroarenes have double O-radicals character that makes them powerful electrophilic species.[32] We therefore intended to exploit a plausible stepwise radical [3+1] cycloaddition with an electron-rich P(III) reagent to promote their deoxygenation. This process should deliver the corresponding aryl nitroso (not shown; see supplemental information) that ought to undergo another round of photochemical deoxygenation to the key singlet nitrene **II**.[33,34] This mild photochemical strategy obviates for the use of dangerous azides as well as harsh thermal conditions, which are the state of the art in singlet nitrene-generation chemistry. At this point, **II** would lead the formation of an azirine **III**, thus establishing a key C–N bond between the former nitro group *N*-atom and the *ortho*-carbon in the original starting material (labeled with a red •).[35] A 6π electrocyclic ring opening would then lead to the seven-membered ring ketimine **IV**, which is strained activated and can be trapped by an amine nucleophile, such as Et_2NH.[36] This step creates the second key C–N bond in the *ortho*-phenylenediamine as the amine coupling partner is now linked to the former nitro-bearing carbon (labeled with a blue •).[37] This process generates the 1*H*-azepine **V** that readily isomerizes to the thermodynamically more stable 3H-isomer **VI**.[38] At this point, we hoped that the addition of an electrophilic trapping agent, such as trifluoroacetic anhydride (TFAA), would take place at the azepine N-atom, thus giving, after enolization, the antiaromatic **VII** that cannot isomerize.[24] This strong thermodynamic perturbation ought to trigger a second 6π electrocyclic reaction, this time in a closing direction, to give the *N*-TFA aziridine VIII. The push-pull nature of this system should result in a facile aromatization to the *ortho*-aniline **1b**, where the Et_2N functionality is linked to the initial nitro-bearing carbon, whereas the nitro group has been shifted to its starting *ortho* position, reduced, and amidated.

Pleasingly, this proposal could be achieved by implementing a one-pot procedure where **1a** and **1c** initially reacted with $P(O\textit{i}\text{-}Pr)_3$ in acetonitrile solvent under blue light-emitting diode (LED) irradiation (λ = 427 nm) and then in the dark with TFAA. Under these mild conditions, **1b** was obtained in 73% yield. The advantage of using TFAA as the activator and aniline-protecting group is also that, upon simple basic workup, the method provided access to free aniline **2b**. The use of 427 nm wavelength is crucial in achieving high yields for the conversion of **1a** into the desired 3*H*-azepine **VI**. Indeed, although nitroarenes often feature a stronger absorbance in the 370–390 nm range, the use of light sources centered on these wavelengths can also lead to the photoexcitation of **VI**, which leads to decomposition pathways.

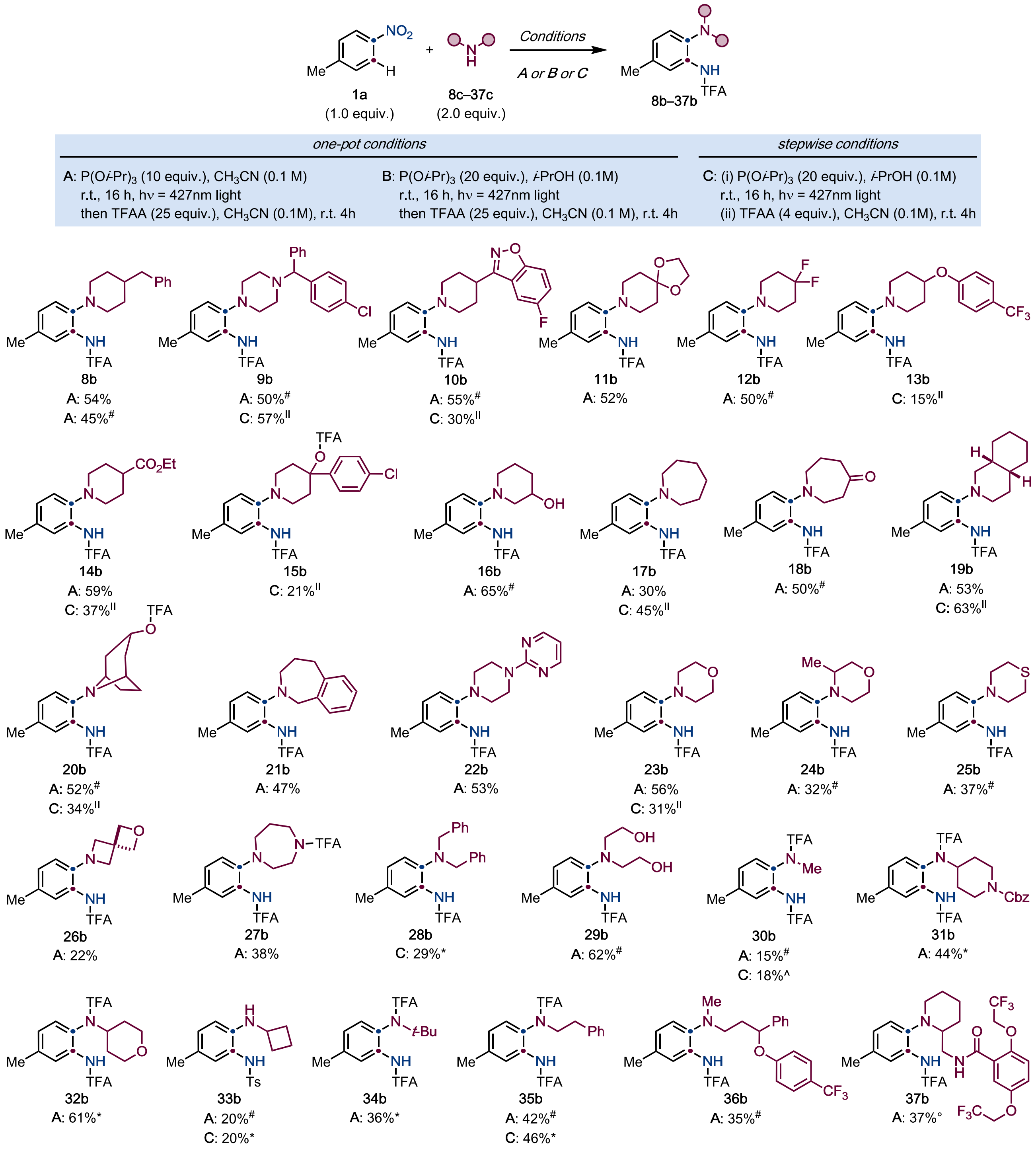
In terms of scalability and use of other electrophilic partners, the 3*H*-azepine intermediate **VI** has been prepared on 5.0 mmol scale, and its aromatization was performed using other reagents, which enabled the introduction of commonly used protecting groups, such as Bz (**3b**), Ts (**4b**), and Cbz (**5b**), into the desired *ortho*-phenylenediamines. More remarkably, we also succeeded in activating **VI** with alkyl electrophiles, such as Me–OTf and Me–I, that, depending on the reaction conditions, selectively provided the mono- and the di-methylated anilines **6b** and **7b**, respectively. These preliminary results demonstrate the potential of this strategy for the streamlined construction of *ortho*-phenylenediamine featuring two different alkyl amine substituents, something particularly difficult to achieve with any previous protocols.

Scope of the process

With a set of optimized conditions in hand, we were keen on assessing the generality of the method in preparing *ortho*-phenylenediamines. From this perspective, our interest was mostly focused on introducing high-value amines (Scheme 2) as well as targeting difficult-to-access poly-substituted aromatic scaffolds (Scheme 3).[13,39]

Amine scope

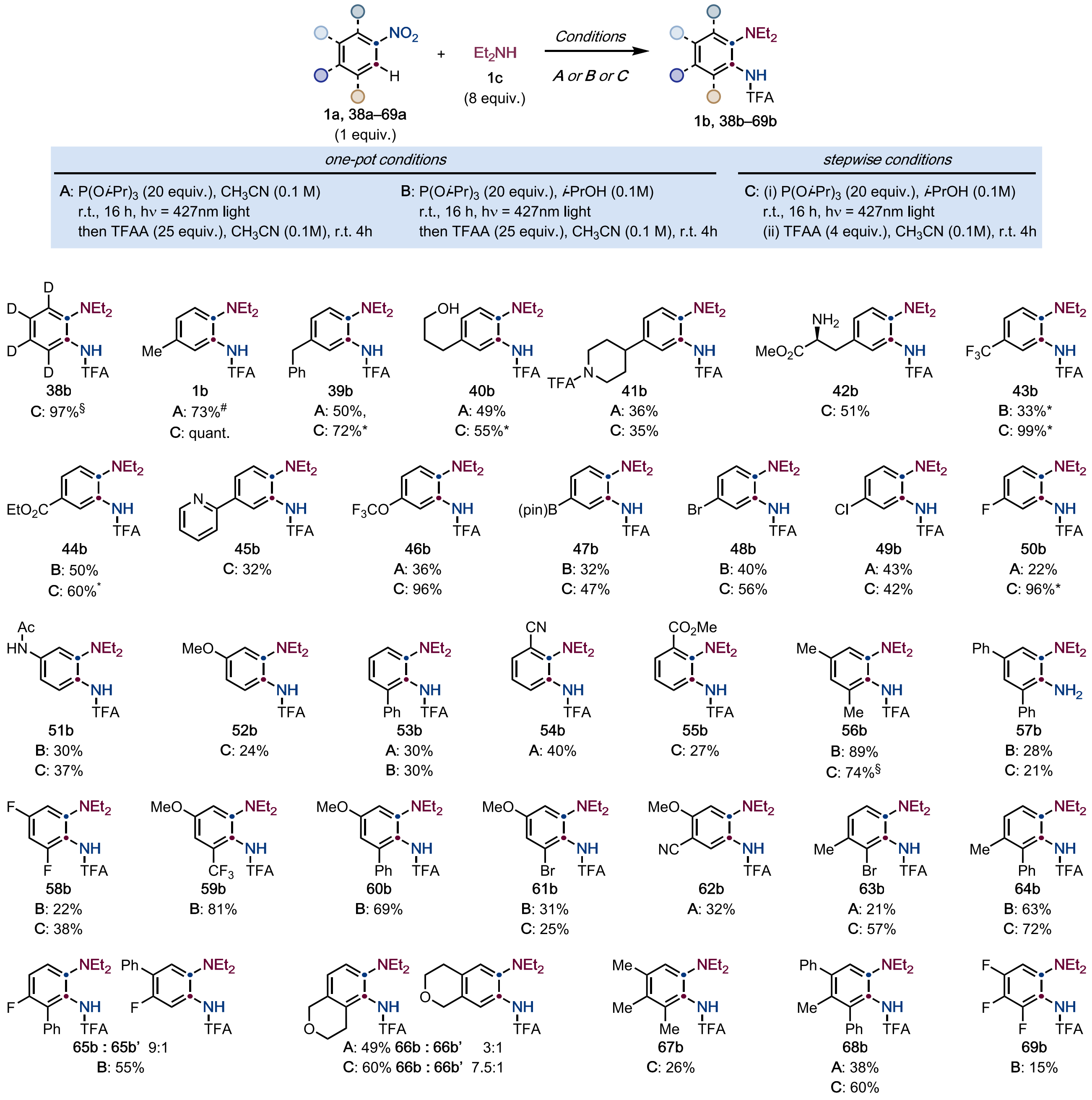
We undertook amine scope exploration with the objective of incorporating structurally complex and densely functionalized drug-like derivatives (Scheme 2). This broad



Scheme 2. Amine scope using 1a as the nitroarene

#, 1 equiv R_2NH, 2 equiv **1a**; ‖, CH_3CN was used as solvent for the 1° step; *, 8 equiv R_2NH, 20 equiv P(O*i*-Pr)$_3$; °, 20 equiv P(O*i*-Pr)$_3$; ^, 16 equiv $MeNH_2$ in EtOH, 20 equiv P(O*i*-Pr)$_3$. See supplemental information for more details.

structural diversity, however, means that both steric and electronic factors can come into play in the reaction sequences and challenge the reactivity. Therefore, although the previously discussed reaction conditions can be used to access the desired



Scheme 3. Nitroarene scope using 1c as the amine

§, Reaction performed under purple LEDs ($\lambda = 390$ nm) irradiation; *, reaction performed using 32 equiv of **1c** and 30 equiv of $P(Oi\text{-}Pr)_3$; #, 1 equiv R_2NH, 2 equiv nitroarene. See supplemental information for more details.

products, modifications are sometimes required to maximize the reaction yields (Scheme 2, conditions A, B, and C).

Piperidine is the most commonly used saturated *N*-heterocycle in drug discovery campaigns,[3] and our method enabled the efficient incorporation of both C4- and C3-functionalized substrates (**8b–16b**). This demonstrated compatibility of photoexcited nitroarene and singlet nitrene chemistry with HAT (H-atom transfer) activated benzylic (enthalpic effects; **8b** and **9b**) and α-O/N (polar effects; **9b** and **13b**) C(sp^3)–H bonds, electron-rich acetal and aryl ether functionalities (**11b** and **13b**) as well as a *gem*-difluoro motif (**12b**), ester (**14b**), and free alcohol (**16b** and **15b**; including somewhat labile tertiary benzylic ones) groups. The successful formation of **12b** and **14b** is relevant because the ester and *gem*-difluoro functionalities are often inserted into *N*-heterocycles with the intention of lowering the piperidine basicity and nucleophilicity. Furthermore, the amines leading to the formation of **10b** and **15b** map the structure of many antipsychotic drugs, such as haloperidol and risperidone, respectively.

We then applied the method to other MedChem-relevant *N*-heterocycles, such as decahydroisoquinoline (**19b**), azepane (**17b**, **18b**, and **21b**), and a derivative of the anticholinergic alkaloid tropine (**20b**). The successful formation of **18b**, which features ketone functionality, is noteworthy because classical methods based on S_NAr followed by nitro reduction require additional protection/deprotection steps.

We then looked at other high-value amine coupling partners and successfully extended the reactivity to piperazine (**22b**), the second most common heterocycle in drugs,[3] morpholines (**23b** and **24b**), thiomorpholine (**25b**), a spirocyclic morpholine bioisoster (**26b**), and a protected 1,4-diazepane (**27b**), also a motif often encountered in the structure of many medicines.

Acyclic secondary and primary amines were evaluated next, and they generally provided the desired *ortho*-phenylenediamines in good-to-moderate yields (**28b–35b**). In the case of the primary amines, further trifluoroacetamide (TFA) protection of the NH functionality took place. This effort demonstrated compatibility with methyl amine (**34b**), protected piperidine (**31b**), and tetrahydropyran (**30b**) units, as well as sterically hindering cyclobutyl (**33b**) and *t*-butyl (**35b**) amines. Phenylethylamine, which is a common structural feature among neurotransmitters and hormones (e.g., dopamine and adrenaline, respectively), was efficiently introduced (**32b**). The limitation of this methodology currently lies in the use of anilines, most likely due to their decreased nucleophilicity, which does not enable fast trapping of the ketimine **IV** as soon as it is formed.

As a finale element of amine scope evaluation, we used the protocol for the late-stage *ortho*-phenylenediamine formation using the structurally complex blockbuster drugs fluoxetine (antidepressant) and flecanide (antiarrhythmic agent), which gave **36b** and **37b** in moderate yields.

Aromatic scope

Having evaluated the scope of amines compatible with the reactivity, we explored the types of aromatic substitution patterns that could be targeted by the process (Scheme 3).

The utilization of per-deuterated nitrobenzene resulted in the formation of isotopically enriched **38b** in high yield. *Para*-substituted nitroarenes were used to access a series of 1,2,4-tri-substituted *ortho*-phenylenediamine (**1b** and **39a–50a**). This included several alkyl groups (primary and secondary, **1b** and **39b–43b**), including an L-amino acid unit (**42b**), several electron withdrawing functionalities (by both inductive [**43b** and **46b**] and resonance [**44b**] effects), and a C2-pyridyl substituent (**45b**). Successful reactivity with *para*-B(pin)-, *para*-Br-, and *para*-Cl-nitrobezenes gave **47b–49b** that can be engaged in standard cross-coupling chemistry to further downstream C(sp^2)–C, as well as C(sp^2)–N and C(sp^2)–O bonds. Noteworthy, *para*-F-nitrobenzene provided the fluorinated *ortho*-phenylenediamine **50b** despite its intrinsic activation toward S_NAr reactivity.

Meta-substituted nitrobenzenes were evaluated next, and they provided access to products mapping the 1,2,4- or 1,2,3-pattern, depending on the electronic nature of the substituent.[24,40–42] *Meta*-NHAc and *meta*-OMe derivatives gave the 1,2,4-derivatives **51b** and **52b** in moderate yields, whereas the *meta*-Ph provided access to 1,2,3-*ortho*-phenylenediamine **53b**. The preparation of **51b** demonstrates access to a tri-aniline derivative where all *N*-moieties are differentiated. The ability of the methodology to target the preparation of 1,2,3-trisubstituted benzenes from *meta*-substituted nitrobenzenes is also noteworthy in the broader context of C–H activation/functionalization chemistry. Indeed, both directed and non-directed methods based on either organometallic, ionic, or radical intermediates provide almost exclusively the 1,2,4-pattern in order to avoid steric strain.[13]

A different type of 1,2,3-benzene substitution pattern to the one of **53b** was obtained using *ortho*-substituted nitrobenzenes that gave **54b** and **55b**, where the aromatic substituent is next to the newly introduced Et_2N-group. Although these examples were formed in moderate yields, it is worth considering that (1) ring expansion of *ortho*-substituted singlet nitrenes is a renowned challenge in the field, and (2) in these cases, amine addition to ketimine **IV** occurs at sites of relatively high steric hinderance.[43]

The synthesis of *ortho*-phenylenediamines across poly-substituted nitroarenes was evaluated next. We were particularly interested in the possibility of accessing derivatives featuring 1,2,4,5- and/or 1,2,3,4- and/or 1,2,3,5-tetrasubstituted systems. Aromatic molecules featuring these patterns are highly sought-after by many industrial sectors (e.g., pharma, agro, and materials) because multiple contiguous substituents impart a three-dimensional (3D) sphere-like shape to the aromatic, in contrast to the more typical planar or rod-like shapes. Despite this relevance, preparing molecules featuring these substitution patterns is still challenging because increased steric hindrance retards traditional aromatic functionalization reactivities. Our investigation started with the evaluation of symmetrical *meta*,*meta*-disubstituted nitrobenzenes that provided the 1,2,3,5-tetrasubstituted derivatives **56b–58b** in good yields. Furthermore, substrates containing two different *meta* substituents could also be used, leading to the desired products **59b–61b** in high positional selectivity.

Para,*meta*-disubstituted derivatives were evaluated next, and in this case, the desired *ortho*-phenylenediamine products were obtained in generally good selectivity, depending on the nature of the substituents. Specifically, *meta*-MeO-*para*-CN-nitrobenzene gave **62b** (1,2,4,5 pattern), whereas *meta*-Br-*para*-Me- and *meta*-Ph-*para*-Me-nitrobenzenes exclusively led to **63b** and **64b** (1,2,4,5 pattern). *Meta*-Ph-*para*-F-nitrobenzene and the bicyclic nitroisocromane resulted in a mixture of products (**65b** and **65b′** and **66b** and **66b′**, respectively) that however strongly favored the 1,2,3,4 pattern. Moreover, we benchmarked our reactivity to target the assembly of *ortho*-phenylenediamines featuring a pentasubstituted aromatic core. Pleasingly, *meta*,*para*,*meta*-trisubstituted nitroarenes led to the formation of highly congested derivatives **67b–69b** in moderate yields. **69b** is a noteworthy endpoint of this poly-substituted arene exploration because it represents one of the most activated substrates for S_NAr reactivity, which, however, was funneled into the desired photochemical pathway, thus leaving untouched the activated C(sp^2)–F bonds.

Conclusions

The results reported here provide a distinct strategy for the direct assembly of complex and high-value *ortho*-phenylenediamines from nitroarenes and amines. This method, which requires simple blue light irradiation at room temperature, engages complex primary and secondary amines and provides access to synthetically challenging poly-substituted aromatic derivatives. Furthermore, the seemingly substitution reactivity whereby the amine displaces the nitro group, which, in turn, undergoes a series of 1,2-shift reduction and functionalization, provides an alternative retrosynthetic logic that streamlines the assembly of these high-value materials.

EXPERIMENTAL PROCEDURES

Resource availability

All experimental procedures are detailed in the supplemental information.

Lead contact

Further information and requests should be direct to and will be fulfilled by the lead contact, Daniele Leonori (daniele.leonori@RWTH-aachen.de).

Materials availability

All reagents in this study are either commercially available or can be easily prepared as indicated in supplemental information.

Data and code availability

All data for the replication of this work are given in the supplemental information or can be obtained by the lead contact upon reasonable request.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2023.10.008.

ACKNOWLEDGMENTS

R.S.-B. thanks the European Union Horizon 2020 innovation program for the Marie Skłodowska-Curie grant agreement no 956324 (PhotoReAct). B.R. thank Janssen for a PhD CASE Award.

AUTHOR CONTRIBUTIONS

A.R. and D.L. designed the project and supervised the work. R.S. and B.R. conducted the experiments. All authors analyzed the data and wrote the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: April 19, 2023
Revised: July 26, 2023
Accepted: October 16, 2023
Published: November 14, 2023

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